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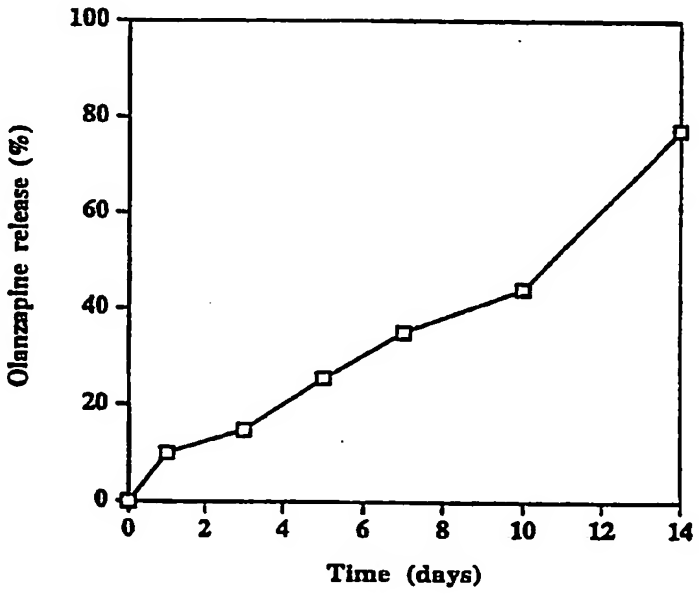

(57) Abstract

There is provided a pharmaceutical composition comprising polymeric microparticles including a drug and a fatty acid, which composition may be adapted to provide a release rate of drug that is approximately linear with time, and to provide no significant burst effect.

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CONTROLLED RELEASE MICROSPHERE DELIVERY SYSTEM

Field of the Invention

This invention relates to a new drug delivery composition comprising biodegradable microspheres and/or microcapsules, which are useful, in particular, in the parenteral delivery of drugs.

Background to the Invention

Olanzapine is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]-benzodiazepine. It is a serotonin ($5\text{-}HT_2$) and dopamine (D_1/D_2) receptor antagonist with anticholinergic activity. The preparation of olanzapine has been described in US 5,229,382 (which document is hereby incorporated by reference). The comparative pharmacology of the compound has been reviewed by N. A. Moore *et al*, Curr. Opin. Invest. Drugs 2, 281 (1993). The drug is currently marketed as an oral tablet formulation that is taken on a daily basis.

The encapsulation of drugs into polymeric microspheres is a well established technology, which has been described in various reviews and books (e.g. Deasy, Microencapsulation and Related Drug Processes, Dekker, New York, 1987 and Chasin and Langer, Biodegradable Polymers as Drug Delivery Systems, Dekker, New York, 1990). A wide variety of drugs have been incorporated into polymers such as polylactide coglycolide, including low molecular weight conventional drugs, as well as peptides and proteins. The purpose of encapsulation is normally to provide a sustained or controlled release of a therapeutic agent or an antigen.

Microencapsulation processes based on emulsification and solvent removal are well known in the art (US 3,523,906, US 3,523,907, US 3,960,757). In US 3,691,090, an organic solvent is evaporated from a dispersion of microparticles contained in an aqueous medium.

US 4,389,330 and US 4,530,840 describe the preparation of microparticles containing an active agent. The active agent and wall-forming agent are dissolved in a common solvent. The solution is then dispersed in a suitable non-miscible medium such as water. The solvent is then evaporated to form microparticles containing the active agent. The final residual solvent can be removed by an extraction process. The particles can be of sizes ranging from below 1 to 100 μm or larger. These prior art documents do not mention the use of a fatty acid in the formulation of controlled release microparticle systems.

The use of polylactide coglycolide materials for the controlled delivery of neuroleptic agents has been described for drugs such as haloperidol (WO 94/10982), respiridone (WO 95/13814) and fluphenazine (Ramtoola *et al* J. Microencaps. 2, 415 (1992)). The encapsulation of chlorpromazine in polylactide has been described by Suzuki and Price. J. Pharm. Sci. 74, 21 (1985). Sustained release microspheres containing antipsychotic agents are disclosed in Chem. Abs. 121(6) Abstract 65597, by Shigeni *et al*. However, none of these references disclose formulations comprising a fatty acid.

The use of carboxylic acid salt surfactants as emulsifiers in oil in water emulsions used for the preparation of microspheres with a particulate core formed from biodegradable polymers such as polylactide and poly(lactide coglycolide) has been described in the prior art, e.g. US 4,384,975 and

Fong *et al*, J. Controlled Release 1, 119, (1986). In these articles the drug was dispersed in a polymer solution (comprising an organic solvent) and an aqueous solution (containing sodium oleate or potassium oleate as an emulsifier). However, the use of free fatty acids as a component of the microspheres is neither mentioned nor suggested.

In the conditions for which drugs such as olanzapine find utility, such as schizophrenia, patient compliance is of vital importance. It is often observed that patients refuse to take oral medication for reasons associated with the symptoms of their condition. To improve patient compliance, it would therefore be of benefit to develop long acting e.g. intramuscular formulations of such drugs. In this respect, it is thus expected that a controlled release formulation of drugs such as olanzapine for intramuscular or subcutaneous administration, which provided steady plasma levels of drug, would be advantageous, especially if such a formulation were capable of providing a steady, yet sufficiently high, level of drug to enable practical control of the disease.

It is well known that the encapsulation of a drug such as olanzapine into a microsphere formulation in high quantities may give rise to an initial high release of drug (i.e. a burst effect). (Indeed, the applicants have confirmed this to be the case in experimentation (see below).) Such a burst effect may result in unacceptable side effects, including problems associated with toxicity of the drug and (for drugs such as olanzapine) sedation.

Surprisingly, we have now discovered that a novel microparticle formulation comprising a drug (e.g. a basic drug, such as the neuroleptic drug, olanzapine), a polymer, such as polylactide coglycolide, and a fatty

acid, can be prepared, and may provide a formulation which produces little to no burst effect, as well as zero order release of drug over extended time periods.

We have found that, when a simple technique, such as an oil in water emulsification procedure, is employed to incorporate drugs such as olanzapine into polymeric (e.g. polylactide coglycolide) microparticles, without the presence of a fatty acid, an unacceptable burst effect is produced. Conversely, we have found that microparticulate compositions including fatty acids, basic drugs (and, more particularly, neuroleptic agents) in biodegradable polymeric microparticles, not only improve the loading of drug into the microparticles, but may also provide a minimal initial burst of drug, and an approximate (i.e. substantially) linear release of drug. Such compositions have not been described in, or suggested by, the prior art.

Description of the Invention

According to the invention there is provided a pharmaceutical composition comprising polymeric microparticles including a drug mixed with a fatty acid (referred to hereinafter as "the compositions of the invention").

The compositions of the invention may, in particular, comprise biodegradable and/or biocompatible microparticles containing a basic drug, more particularly a neuroleptic drug, such as a thienolbenzodiazepine (e.g. olanzapine), and a fatty acid.

We prefer that the drug is a weak base. By "weak base", we include compounds with a pKa of less than 10.5.

The compositions of the invention may be prepared by dispersing drug and fatty acid in a polymer solution, using standard surfactant aqueous solutions as emulsifiers.

In particular, the compositions of the invention may preferably be produced by emulsification of a solution of a biodegradable polymer and fatty acid that will provide a wall forming material or matrix material. In such a procedure, the polymer and the fatty acid are first dissolved in a suitable organic solvent and then dispersed as an oil in water emulsion in an aqueous environment, or as an oil-in-oil emulsion in a non-aqueous environment. Solid particles can be produced by a suitable process such as solvent evaporation or spray drying wherein the organic solvent is removed.

Drugs that are suitable for use in the compositions of the invention include, but are not limited to, neuroleptics such as thienolbenzodiazepines (e.g. olanzapine), benzodiazepines such as cromazepam, clobazam, diazepam, phenothiazines such as acetophenazine maleate, bromperidol, respiridone, chlorpromazine, chlorprothixene, haloperidol, fluphenazine, fluspirilene, sex hormones such as danazol.

The term "neuroleptic" will be well understood by those skilled in the art (see, for example, Martindale, "*The Extra Pharmacopoeia*", 31st Edition, Royal Pharmaceutical Society (1996) at page 669 *et seq* and Dorland's Illustrated Medical Dictionary, 28th Edition, W. B. Saunders (1994) at page 110). The term most preferably refers to a compound selected from the group consisting of haloperidol, clozapine, respiridone, amisulpride, Seroquel® (quetiapine), sertindole, ziprasidone, zotepine, and olanzapine.

The most preferred neuroleptic is olanzapine. The term "neuroleptic" includes both basic and acidic drugs; however basic, especially weakly basic, neuroleptics are preferred.

Particularly useful polymeric materials which may be used in the compositions of the invention include polylactide coglycolide (PLG). PLG can be obtained from known suppliers (for example Boehringer Ingelheim) in a range of molecular weights and molar ratios of polylactide to polyglycolide. PLG is preferred because of its established regulatory status and the fact it degrades to materials that can enter the metabolic pool.

The ratio of lactide to glycolide may be from 85:15 or thereabouts, preferably 75:25 or thereabouts, and more preferably 50:50. A preferred molecular weight for PLG polymer materials is in the range of from about 4 to 50 kD as determined by the Mark Houwink Equation (MHE) and 20 to 150 kD as measured by gel permeation chromatography using polystyrene standards. When the characteristics of the polymer are given in terms of intrinsic viscosity, a preferred range is 0.2 to 1.2 dl/g.

Suitable fatty acids which may be employed in the compositions of the invention include compounds comprising a saturated or unsaturated, linear or branched, acyclic hydrocarbon chain containing one or more carboxyl group. A range of fatty acids, including those with chain lengths from C_8 to C_{24} may be used in the present invention; however chain lengths from C_{14} to C_{20} are preferred.

A preferred fatty acid is oleic acid. Commercially available oleic acid may consist mainly of octadec-9-enoic acid and also contains some stearic and

palmitic acids. Ricinoleic acid is another preferred material. Commercially available ricinoleic acid may consist mainly of 12-hydroxy-9-octadecenoic acid but also contains other fatty acids obtained from the hydrolysis of castor oil from which ricinoleic acid is derived.

Suitable concentrations of fatty acids in the compositions of the invention are in the range 1 to 50% w/w, (i.e. wt%, expressed as a percentage of the weight of the microparticle), preferably 5 to 30% w/w and most preferably 10 to 20% w/w. Suitable concentrations of polymer materials in the compositions of the invention are in the range 5 to 98% w/w (wt%, expressed as a percentage of the weight of the microparticle), preferably 10 to 96% w/w and most preferably 20 to 90% w/w.

The compositions of the invention provide not only a high loading of the drug (greater than 10% w/w expressed as a percentage of the final formulation), but may also provide an approximate linear release of drug over, for example, 30 days or more *in vitro*, and may also provide no significant burst effect.

By "approximate linear release", we include that the release follows essentially zero order kinetics and a plot of release rate against time can be best represented by a straight line relation. Permissible deviations from that straight line are in the range 0 to 50%, preferably 0 to 25% and more preferably 0 to 10%, over the main part of release of the drug from the composition following administration. In other words, by "approximate linear release", we include that the rate of release of drug is essentially constant over the main part of the time over which drug is released following administration. Permissible deviations from "constant" are in the range 0 to 50%, preferably 0 to 25% and more preferably 0 to 10%, at

any one time over the main part of release of the drug from the composition following administration. By "main part" of release of the drug, we mean the part between any initial burst which may occur e.g. during the first day following administration, and any "tailing off" of release which may occur at the end of release. The main part of the release will typically constitute at least 80%, preferably at least 90%, of the total time over which drug is released.

The term "no significant burst effect", includes that no more than 30%, preferably no more than 25%, more preferably no more than 23%, and especially no more than 20%, of the loaded drug is released in one day (i.e. the first day following administration), as measured in an *in vitro* dissolution test using, for example, phosphate buffered saline as the release medium (e.g. as described below).

Compositions of the invention may provide an approximately linear release of drug over time, and may provide no significant burst effect. Moreover, compositions of the invention may be readily adapted to provide an approximately linear release, and to provide no significant burst effect, in accordance with techniques such as those described hereinafter.

The compositions of the invention may be of a size range suitable for injection, such as between 1 and 500 μm, preferably between 20 and 150 μm, as measured by a suitable technique, such as laser diffraction.

The route of administration and release rate often dictate the preferred size of the microparticle. Similarly, the choice of polymer (e.g., in the case of PLG, in terms of the ratio of lactide to glycolide), and the molecular

weight of the polymer, can be employed to obtain different release rates of encapsulated material. Further, fatty acid content and choice of fatty acid can provide further control over release rates of encapsulated material.

The microparticles can be administered using methods known in the art. Most preferably, the microparticles can be administered parenterally.

As used herein, the term "microparticles" includes microspheres, microcapsules and the like. We use the term "microsphere" herein to describe a particle where the drug is distributed throughout (e.g. uniformly in) the polymer matrix. We use the term "microcapsule" to describe a particle where the drug is contained (e.g. as crystals) in the core of the microparticle and the polymer acts as a coating or shell.

The properties of microspheres and microcapsules can be controlled by the choice of polymer, fatty acid and the quantity of drug to be encapsulated in the polymer particle.

Suitable dosing regimens for a particular drug can be determined readily by a physician or the skilled artisan based on the patient's condition and the properties of the drug. For example, a preferred dosage for olanzapine is from about 1 to about 25 mg/kg. More preferably the dosage is from about 5 to about 10 mg/kg.

The compositions of the invention may be administered to a mammal in suitable dosage forms, in accordance with techniques, and *via* delivery devices, all of which are known to those skilled in the art. However, we prefer that the compositions of the invention are administered parenterally. By the term "parenteral administration", we include the delivery of the

composition by injection to a warm blooded animal by subcutaneous, intramuscular, intravenous, epidural or intrathecal routes or such methods as are known to the skilled artisan. The more preferred routes of administration are subcutaneous and intramuscular.

The compositions of the present invention may comprise polymeric biodegradable and biocompatible microparticles designed to provide an effective amount of the active ingredient (i.e. the drug; such as a neuroleptic) over an extended period of time. A preferred embodiment is the administration of a single dose of the microparticles loaded with drug to release the drug over an extended period of time, thus avoiding the necessity of repeated injections.

The present invention provides the controlled delivery of a drug, such as a neuroleptic, over a period ranging from 5 to 100 days depending on the microparticle system selected. A preferred embodiment provides release over the period from about 10 to about 50 days or more particularly over the period from about 20 to about 40 days. The duration of action can be controlled by appropriate choice of polymer, microsphere particle size, fatty acid choice and drug loading. A further preferred embodiment is release over the period of from about 14 to about 30 days. By "about", we include plus or minus 5 (e.g. 2) days in respect of the lower limits of the above-quoted release period ranges, and plus or minus 10 (e.g. 5, preferably 2) days in respect of the upper limits of the above-quoted release period ranges.

The wall forming or matrix polymer can be chosen from a range of materials known to those skilled in the art that includes polylactides, polyglycolic acid, copolymers of polylactide and polyglycolide,

polycaprolactones, polyalkanoic acids, (particularly mixtures of polyhydroxybutyrate and polyhydroxyvalerate), polyorthoesters, polyanhydrides. A preferred polymer is polylactide coglycolide (PLG) and a preferred ratio of lactide to glycolide is about 50:50. The molecular weight of the selected polymer will be chosen after considering the fatty acid to provide the required release rate. Suitable molecular weights for the polymers are in the range 2 to 100 kD. The preferred material (polylactide coglycolide) has a molecular weight (inherent viscosity) in the range of from 9 - 50 kD or thereabouts. A especially preferred molecular weight range is 25 kD or thereabouts.

The polymers can be used singularly or in combination. A preferred material is the copolymer polylactide coglyclide (PLG).

The microparticles may be produced by a suitable emulsification (oil in water) method followed by a solvent removal process, or other processes known to the skilled artisan. The solvents can include those that are non-miscible with aqueous environments and include ethylacetate, benzyl alcohol, dichloromethane and halogenated hydrocarbons. Preferred solvents are dichloromethane and ethyl acetate. Other processes which may include spray drying, coacervation, solvent evaporation, heat and/or cooling congealing, supercritical fluid, and other methods recognised by the skilled artisan, may be used.

A preferred method for preparation of the microparticles is by emulsion solvent evaporation method. The drug, the fatty acid and the polymer (e.g. polylactide coglycolide (PLG)) are co-dissolved in an appropriate solvent, such as dichloromethane to form the oil phase. This oil phase is mixed with an aqueous solution containing an emulsifier, such as

polyvinyl alcohol, and emulsified. A stirrer may be used to assist the emulsification process. The emulsion may be stirred for up to 24 hours at room temperature for the solvent evaporation to take place. The microparticles may be collected by an appropriate means, such as centrifugation, washed with an appropriate solvent, such as water and dried (e.g. by freeze drying). The dried particles may be passed through sieves to collect a suitable size fraction.

The emulsion may be (and normally is) stabilised by a suitable emulsifying agent. Materials which may be employed to this end include polyvinyl alcohol, polyvinyl pyrollidone, bile salts and non-ionic surfactants. A preferred emulsifier material is polyvinyl alcohol. A suitable concentration is from 0.25 to 7% w/v. A preferred concentration is from 1 - 3% w/v. The size of the resultant particle may be controlled by the processing conditions including stirring rate, organic/aqueous phase volume ratios, size and shape of the processing containers.

A size range from 1 - 500 μm is suitable for parenteral administration. A size in the range 20 to 150 μm, e.g. 60 to 120 μm, is preferred.

The solvent can be removed by evaporation or drying processes or solvent extraction to include the use of supercritical fluids.

The particles may be stored in a dried state and may be mixed with a suitable pharmaceutically acceptable diluent to aid administration. Such diluents include aqueous sodium carboxy methylcellulose solution, with and without stabilisers (such as surfactants (e.g. polysorbates)), sesame oil and migliol A12.

Fatty acids suitable for use in the compositions of the invention include oleic acid, linoleic acid, linolenic acid, ricinoleic acid, capric acid, elaidic acid, lauric acid, stearic acid, palmitic acid, arachidonic acid, docosanedioic acid and polyunsaturated fatty acids such as eicosapentanoic acid and docosahexanoic acid. Oleic acid is a preferred material. Hydroxylated fatty acids may also be employed. Ricinoleic acid (a hydroxylated fatty acid) is another preferred material.

The microparticles can be produced in a sterile form through aseptic processing or treated after preparation with gamma irradiation at a dose of 2 Mrad. or higher.

The loading of the drug in the compositions of the invention will be dependent on the physicochemical properties of the compound but for a lipophilic material, a loading of 1 to 90% (i.e. wt%, expressed as a percentage of the weight of the microparticle) could be expected. By "lipophilic compound", we include a compound with a partition coefficient as measured between 1-octanol and an aqueous buffer at pH 7.0 of more than 10. More preferably, the compositions of the invention may contain from 1 to 50 wt% of active ingredient and most preferably from 10 - 35 wt% of active ingredient.

For the avoidance of doubt, the terms "drug" and "therapeutic agent" are intended herein to include drugs/agents which are suitable for use in the treatment, and in the prevention, of disease.

The compositions of the invention may be used to treat/prevent diseases/conditions in mammalian patients depending upon the therapeutic agent(s) which is/are employed. For the above, non-exhaustive, lists of

drugs, diseases/conditions which may be mentioned include those against which the therapeutic agent(s) in question are known to be effective, and include those specifically listed for the drugs in question in Martindale, "*The Extra Pharmacopoeia*", 31st Edition, Royal Pharmaceutical Society (1996). When the composition according to the invention comprises a neuroleptic drug, the present invention provides a method for treating a warm-blooded animal suffering from or susceptible to psychotic disorders by the parenteral administration of a composition according to the invention.

The used herein phrase "dissolution test" refers to methods familiar to the artisan.

The invention is illustrated, but in no way limited, by way of the following examples, in which:

Figure 1 shows the cumulative release of olanzapine from PLG (50/50; 9 kD) microspheres (particle size ≤ 250 μm) loaded with 28.6% olanzapine; 30.8% olanzapine/7.7% oleic acid; and olanzapine/15.4% oleic acid.

Figure 2 shows the cumulative release of olanzapine from PLG (50/50; 25 kD) microspheres (particle size ≤ 250 μm) loaded with 28.6% olanzapine; 30.8% olanzapine/7.7% oleic acid; and olanzapine/15.4% oleic acid.

Figure 3 shows the cumulative release of olanzapine from PLG (50/50; 9 kD and 25 kD) microspheres (particle size ≤ 250 μm) loaded with 30% olanzapine/15% oleic acid.

Figure 4 shows the cumulative release of olanzapine from PLG (50/50; 25 kD) microspheres (particle size ≤ 150 μm) loaded with 30% olanzapine and 15% of a range of fatty acids.

Figure 5 shows the *in vitro* release of olanzapine from PLG microspheres (particle size ≤ 150 μm) loaded with 30% olanzapine and 15% oleic acid.

Figure 6 shows the plasma concentration of olanzapine in a group of five beagle dogs over time, following administration of from PLG microspheres (particle size ≤ 150 μm) loaded with 30% olanzapine and 15% oleic acid.

Example 1

PLG microspheres (particle size ≤ 250 μm) loaded with 28.6% olanzapine without added fatty acid. (Comparative example to demonstrate that a simple formulation provides an unsatisfactory release profile.)

100 mg of olanzapine and 250 mg of PLG (50/50, 9 kD or 25 kD) were co-dissolved in 2 to 3 mL of dichloromethane to form an oil phase. The oil phase was dropped into 100 to 150 mL of cooled aqueous phase containing 1% polyvinyl alcohol (PVA) and emulsified at 1000 rpm. The resulting o/w emulsion was agitated continuously for 4 h at room temperature. The microspheres were collected by centrifugation, washed with water and freeze-dried. The dried particles were passed through a 250 μm sieve to remove any large aggregation and stored in a desiccator at room temperature. Duplicate samples of drug-loaded PLG microspheres containing about 5 mg of olanzapine were accurately weighed and suspended in two separate 500 mL of pH 7.4 PBS solution. The solutions were incubated at 37°C and gently agitated for 1 minute, twice a day.

At suitable times following the start of the test, 5 mL of supernatant from each solution was removed and passed through a 0.2 μm membrane filter into a screw top vial. Then 5 mL of fresh PBS solution was added to each solution. The samples were evaluated for drug content by a UV method at a wavelength of 228 nm.

The results are shown in Figures 1 and 2. The cumulative release of olanzapine show that the drug is released rapidly from the formulation produced from PLG 50:50, 9 kD and 25 kD molecular weight without added fatty acid. Such particles would not be suitable for administration to patients due to the high initial burst of drug.

Example 2

PLG microspheres (particle size ≤ 250 μm) loaded with 30.8% olanzapine:7.7% w/w oleic acid

200 mg of olanzapine, 50 mg of oleic acid and 400 mg of PLG (50/50; 9 kD or 25 kD) were co-dissolved in 4 mL of dichloromethane to form an oil phase. The oil phase was dropped into 200 mL of cooled aqueous phase containing 1% polyvinyl alcohol (PVA) and emulsified at 1000 rpm. The resultant o/w emulsion was agitated continuously for 4 h at room temperature. The microspheres were collected by centrifugation, washed with water and freeze-dried. The dried particles were passed through a 250 μm sieve to remove any large aggregation and stored in a desiccator at room temperature. The drug release behaviour of the microspheres was determined as in Example 1. Figures 1 and 2 show that the addition of oleic acid at 7.7% reduce the release rate of olanzapine.

Example 3

PLG microspheres (particle size ≤ 250 μm) loaded with 30.8% olanzapine/15.4% w/w oleic acid

200 mg of olanzapine, 100 mg of oleic acid and 350 mg of PLG (50/50; 9 kD or 25 kD) were co-dissolved in 4 mL of dichloromethane to form an oil phase. The oil phase was dropped into 200 mL of cooled aqueous phase containing 1% polyvinyl alcohol (PVA) and emulsified at 1000 rpm. The resultant o/w emulsion was agitated continuously for 4 h at room temperature. The microspheres were collected by centrifugation, washed with water and freeze-dried. The dried particles were passed through a 250 μm sieve to remove any large aggregation and stored in a desiccator at room temperature. The drug release behaviour of the microspheres was determined as in Example 1. Figures 1 and 2 show that the addition of oleic acid at 15.4% w/w reduces the release rate of olanzapine. For the case of the polymer of molecular weight 25 kD there is almost no burst effect and the release profile is essentially linear over a 10 day period.

Example 4

PLG microspheres (particle size ≤ 250 μm) loaded with 30.8% olanzapine/15% oleic acid

A further experiment was conducted to show the effect of the nature of the polymer in drug release profile.

218 mg of olanzapine, 109 mg of oleic acid and 400 mg of PLG (50/50, 9 kD or 25 kD) were co-dissolved in 4 mL of dichloromethane to form an oil phase. The oil phase was dropped into 200 mL of cooled aqueous phase containing 1% polyvinyl alcohol (PVA) and emulsified at 1000 rpm.

The resultant o/w emulsion was agitated continuously for 4 h at room temperature. The microspheres were collected by centrifugation, washed with water and freeze dried. The dried particles were passed through a 150 μm sieve to remove any large aggregation and stored in a desiccator at room temperature. The drug release behaviour was determined as in Example 1. The results in Figure 3 show that a linear release of olanzapine can be obtained using 15% oleic acid and PLG of a molecular weight of 25 kD.

Example 5

PLG microspheres (particle size ≤ 150 μm) loaded with 30% olanzapine and 15% in a range of fatty acids

The 109 mg of oleic acid as in Example 4 was replaced by a range of fatty acids (arachidonic acid, docosahexanoic acid, eicosapentanoic acid, linoleic acid, linolenic acid and ricinoleic acid). The preparation and drug release measurements were conducted as in Example 4. The molecular weight of the PLG polymer was 25 kD in all cases. The results shown in Figure 4 show that different release rates can be obtained by choice of different fatty acids. The essentially linear profile obtained for arachidonic acid, ricinoleic acid and linoleic acid appear to be advantageous.

Example 6

Evaluation of olanzapine microsphere *in vivo* using a dog model

A batch of olanzapine (4 g) for animal testing was prepared as described in Example 4. The polymer was PLG 50:50 of a molecular weight 25 kD. The particles were loaded with 30% w/w olanzapine using 15% w/w oleic

acid. The dissolution behaviour was measured as described in Example 1. The dissolution results are shown in Figure 5. An approximately linear release profile for olanzapine was obtained. An experiment was conducted to measure the quantity of intact olanzapine remaining in the microspheres.

Samples of microspheres were removed from the dissolution medium at 7 and 14 days. The samples were freeze-dried and then assayed by HPLC using a validated method to determine the amount of intact olanzapine. Table 1 provides details of the amount of olanzapine released into the dissolution medium at 7 and 14 days respectively and the quantity of olanzapine remaining in the microspheres as compared to the theoretical amount if the results were corrected for the amount released. It will be seen that all the unreleased olanzapine could be recovered intact from the microspheres.

Table 1: Release and recovery of olanzapine from PLG microspheres.

Time	Olanzapine release	Olanzapine remaining in microspheres	
(days)	(% of encapsulated)	theoretical(%)*	residual (by HPLC)
7	34.9	65.1	65.3
14	77.3	22.7	23.2

*Calculated from the amount of olanzapine released into the dissolution medium and the olanzapine content of the microspheres at the start of dissolution testing.

The olanzapine microspheres were administered intramuscularly to a group of 5 beagle dogs. The microspheres were suspended in a dosing vehicle comprising 2% CMC and 0.15% Tween 80 using a 21 gauge needle. The dose of drug was 5 mg/kg. The plasma concentration of the drug was measured by a validated HPLC method. The results shown in Figure 6 demonstrate that a steady level of drug could be obtained in the required range of 10 - 20 mg/mL over a suitable time period.

Claims

1. A pharmaceutical composition comprising polymeric microparticles including a drug and a fatty acid.

2. A composition as claimed in Claim 1 adapted to provide a release rate of the drug that is approximately linear.

3. A composition as claimed in Claim 1 or Claim 2 adapted to provide an initial release of drug as measured using a dissolution test employing phosphate buffered saline as the release medium of less than 25%.

4. A composition as claimed in any one of the preceding claims wherein the drug is a weak base.

5. A composition as claimed in any one of the preceding claims wherein the drug is a neuroleptic.

6. A composition as claimed in any one of the preceding claims wherein the drug is olanzapine.

7. A composition as claimed in any one of the preceding claims wherein the polymer is a copolymer of polylactic acid and polyglycolic acid.

8. A composition as claimed in any one of the preceding claims wherein the fatty acid is oleic acid or ricinoleic acid.

9. A composition as claimed in any one of the preceding claims wherein the microparticles comprise 1 to 90% w/w of active agent.

10. A composition as claimed in any one of the preceding claims wherein the size of the microparticles is from 1 to 500 microns.

11. A composition as claimed in Claim 10, wherein the size of the microparticles is in the range 20 to 150 microns.

12. A composition as claimed any one of the preceding claims wherein the microparticles contain from 1 to 50 wt % of active ingredient.

13. A composition as claimed in Claim 12 wherein the microparticles contain from 10 to 35 wt % of active ingredient.

14. A pharmaceutical formulation comprising a composition as claimed in any one of the preceding claims and a pharmaceutical carrier.

15. A process for the preparation of a composition according to any one of Claims 1 - 13 which comprises mixing the drug with a fatty acid and encapsulating or dispersing the complex in a polymer material.

16. A method for treating a warm-blooded animal suffering from or susceptible to a psychotic disorder which comprises the parenteral administration of a composition according to any one of Claims 1 - 13, or a formulation according to Claim 14, to such an animal.

17. The use of a composition according to according to any one of Claims 1 - 13 in the manufacture of a medicament for use in the treatment

of a warm-blooded animal suffering from or susceptible to a psychotic disorder.

18. A method for the treatment or prophylaxis of a disease which comprises administration of a composition according to any one of Claims 1 to 13, or a formulation according to Claim 14, including an active ingredient which is effective against said disease, to a patient in need of such treatment or prophylaxis.

19. A method as claimed in Claim 18, wherein the disease is a psychotic disorder.

20. The use of a composition according to any one of Claims 1 to 13 in the manufacture of a medicament for the treatment or prophylaxis of a disease which comprises administration of said composition, including a therapeutic agent which is effective against said disease, to a patient in need of such treatment or prophylaxis.

21. A use as claimed in Claim 20, wherein the disease is a psychotic disorder.

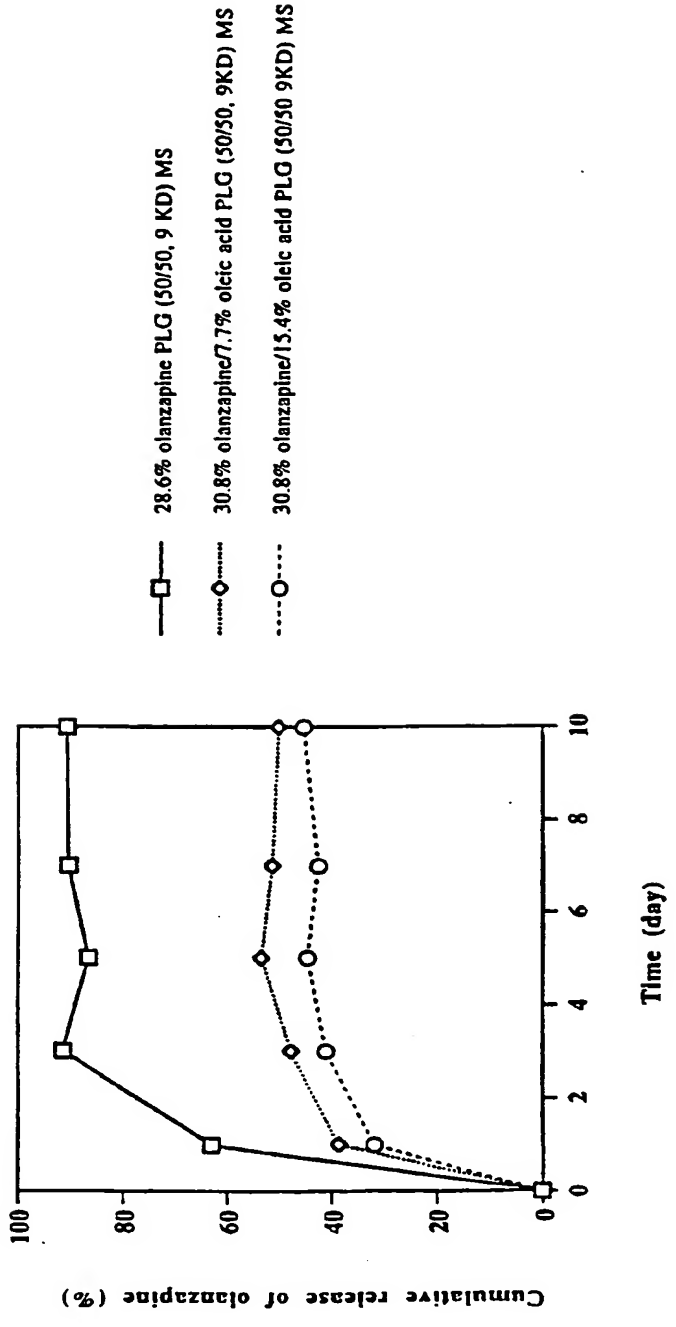

Figure 1

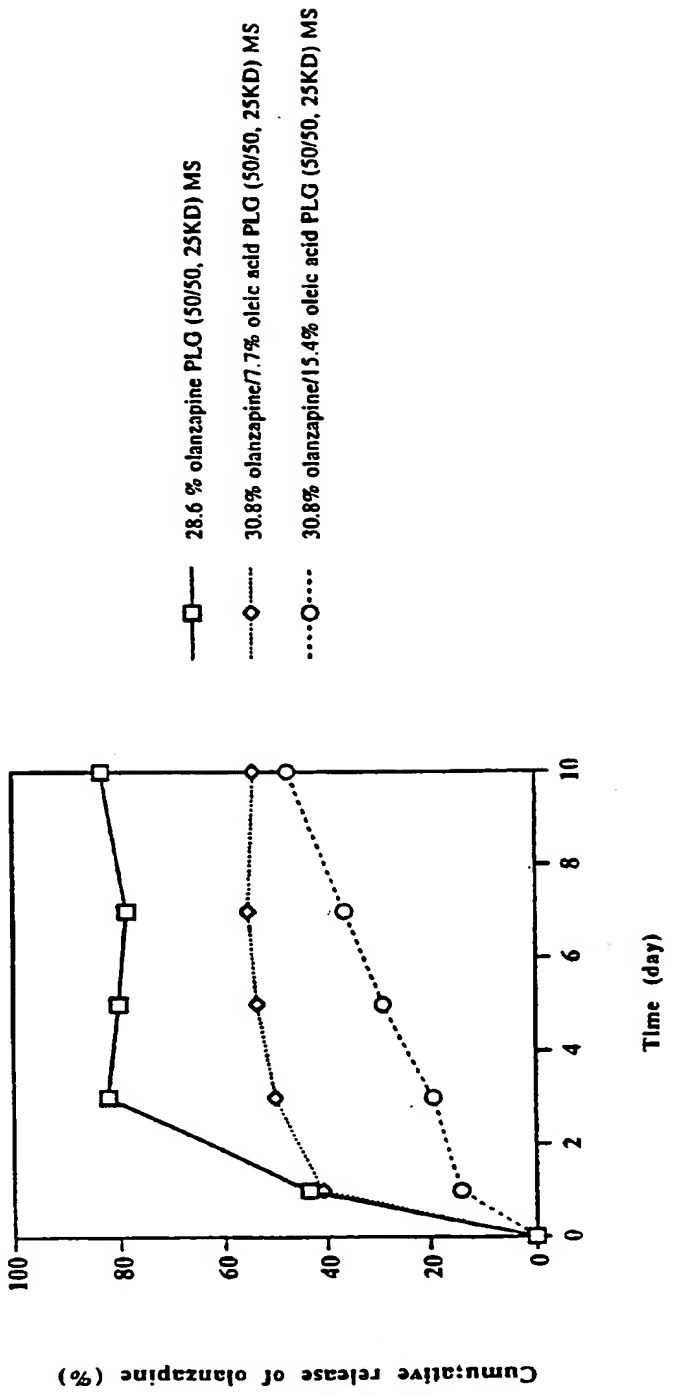

Figure 2

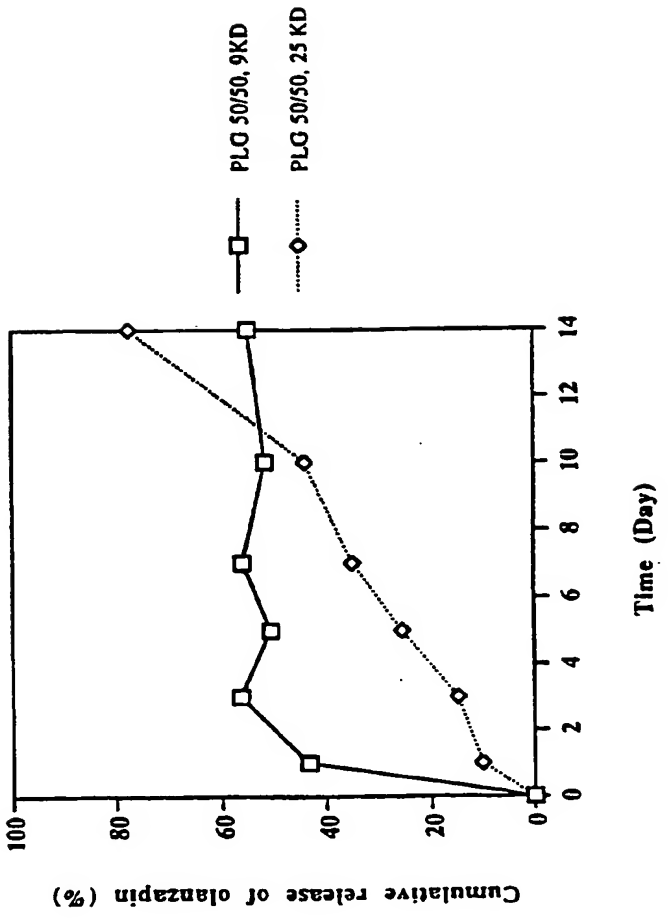

Figure 3

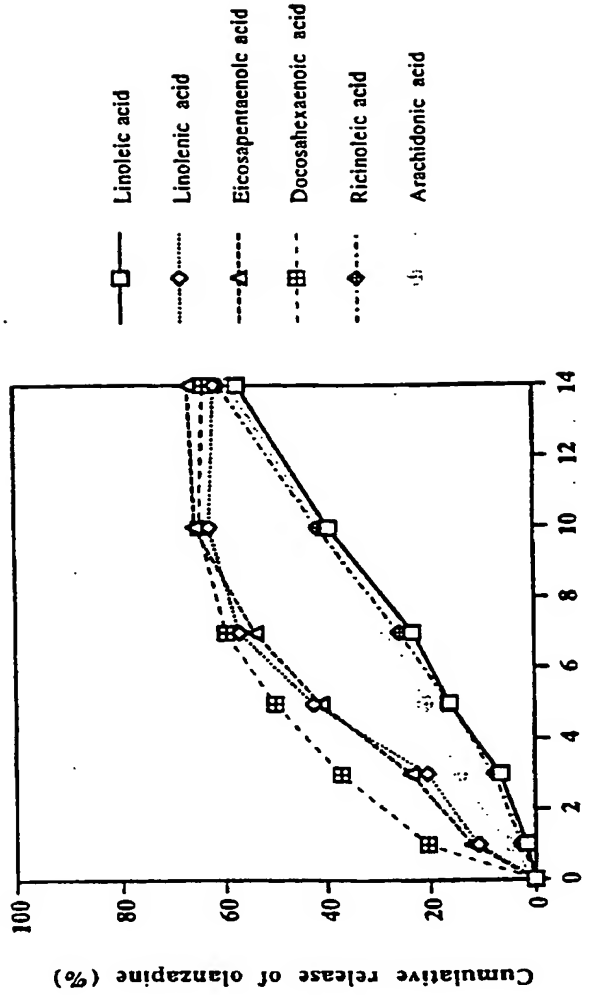

Figure 4

Figure 5

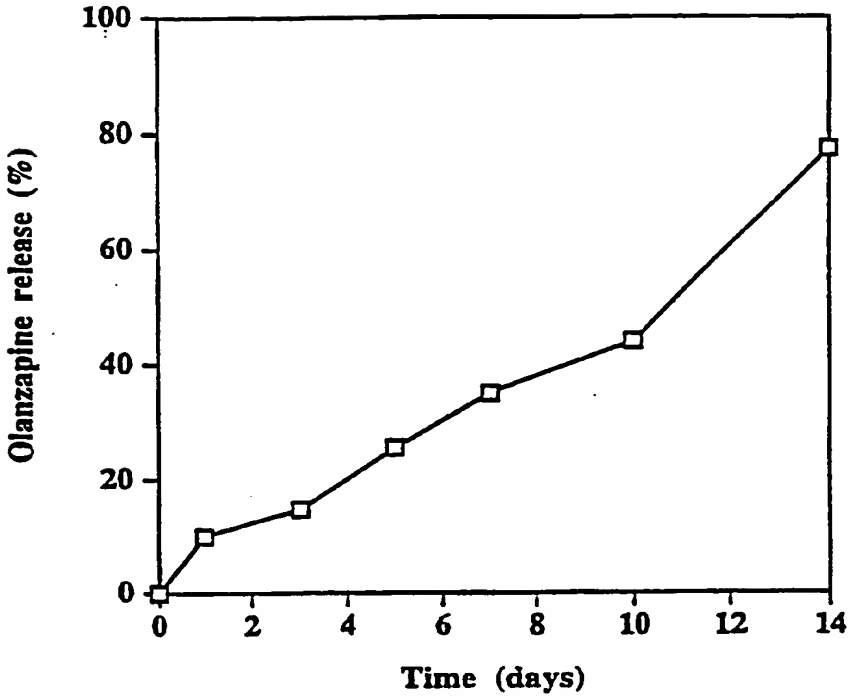

Figure 6